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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/803,954	02/21/1997	KEITH E. LANGLEY	0109063/004	9382

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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	PAPER NUMBER
1647	38

DATE MAILED: 06/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/803,954	Applicant(s) Langley et al
	Examiner Robert C. Hayes, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 15, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *53-67* is/are pending in the application.

4a) Of the above, claim(s) *57-67* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *53-56* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *53-67* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *32*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 8/29/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/803954 is acceptable and a CPA has been established. An action on the CPA follows.

Election/Restriction

2. Applicant's election of Group I (claims 53-56) in Paper No. 37 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 57-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 37.

This application contains claims 57-67 drawn to an invention nonelected with traverse in Paper No. 37. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Applicants are again reminded that because parent application no. 07/355,027 is at the Board of Appeals, and because the Examiner does not have access to the pending claims on

appeal, a double patenting rejection may be necessitated if those claims are directed toward antibodies of metalloproteinase inhibitor products, as in the instant application.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 53 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. For example, the current recitation of "an antibody" encompasses all naturally occurring antibodies that bind metalloproteinase inhibitors; thereby, not involving the hand of man to isolate or purify the antibodies. It is suggested that amending the claims to "an isolated and purified antibody ..." should obviate this rejection.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a single metalloproteinase inhibitor from two distinct species (i.e., bovine and human TIMP-2 of Figures 1 & 2, respectively). No written description of what structurally constitutes any other metalloproteinase inhibitor is disclosed within the specification. No written description of what structurally constitutes any specific epitope required to make a functional monoclonal antibody and their corresponding hybridoma cell line is disclosed within the specification. In contrast, the specification on page 19 merely states that "each monoclonal antibody is directed against a single determinant [epitope] on the antigen", which is further not described. Therefore, one skilled in the art cannot reasonably visualize or predict what critical amino acid residues would structurally characterize the genus of antibodies that "specifically" bind a "metalloproteinase inhibitor", as claimed, or what sequences would comprise a single functional epitope requried to make such antibodies, because it is unknown and not described what structurally constitutes these amino acid sequences/epitopes from any different species, from any different metalloproteinase inhibitor which are further not described; or what functional epitopes even exist in the solely described TIMP-2 polypeptides of Figures 1 & 2. In other words, because it cannot be visualized what specific amino acids constitute these generic metalloproteinase inhibitor sequences/epitopes that are required to make the claimed "specific"

antibodies/monoclonal antibodies and their secreting hybridoma cell lines of the instant invention, the written description requirement under 35 U.S.C. 112, first paragraph are not met.

Applicant is directed toward the Revised Interim Utility and Written Description Guidelines, Federal Register, Vol.64, No.244, pages 71427-71440, Tuesday December 21, 1999.

6. Claims 53-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polyclonal antibodies directed toward the bovine and human TIMP-2 proteins of Figures 1 & 2, respectively, does not reasonably provide enablement for making monoclonal antibodies with unknown epitopes or hybridoma cell lines putatively "secreting" such. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As previously made of record in Paper Nos: 10, 19 & 26, the name "metalloproteinase inhibitor" alone sets forth no structural characterization and little functional characteristics for one of ordinary skill in the art on how to make and use such a protein, which then could be used to make a "specific" antibody (especially when no other specific proteins are disclosed), thereby, requiring undue experimentation to discover such; consistent with the teachings of Rudinger previously made of record.

Second, although the specification generically discusses antibodies on pages 14, 18-19, 48 and 77, no specific monoclonal antibodies nor hybridomas "secreting" such are disclosed

that specifically bind to any metalloproteinase inhibitor, or fragments thereof. In contrast, the specification on page 19 merely states that "each monoclonal antibody is directed against a single determinant [epitope] on the antigen." Similar to the preceding paragraph, the name antibody to a "metalloproteinase inhibitor" sets forth no structural characteristics and little functional characterization for generating antibodies specific to any functional "metalloproteinase inhibitor" protein, and encompasses any antibody directed to any biologically functional equivalent "metalloproteinase inhibitor" polypeptide, or a fragment thereof, as well as those directed toward "deletion analogs, substitution analogs, and addition analogs" thereof. Consistent with that previously made of record, the specification does not teach which particular amino acids are critical for detecting any metalloproteinase inhibitor protein's function, or what amino acid residues constitute a "metalloproteinase inhibitor"-specific epitope; nor how to distinguish such from any different epitope alternatively specific for different proteins. Moreover, random modifications, mutations, substitutions, additions, deletions or truncations of different metalloproteinase inhibitor-related molecules would be expected by the skilled artisan to result in antibodies that cross react with different proteins, or antibodies that no longer recognize the functional metalloproteinase inhibitor protein of the instant invention. For example, Geysen et al. teach that random amino acid changes to a tetrameric peptide/epitope, which includes conservative substitutions to the same antigen, have "frequently been associated with loss of antibody binding" (e.g., pg. 38, 1st col., 2nd *pp*). Thus, the lack of guidance provided in the specification as to what minimal structural requirements are necessary for any specific

metalloproteinase inhibitor antibody binding reaction would prevent the skilled artisan from determining whether any modification or mutation or truncation to the bovine and human TIMP-2 proteins of Figures 1 & 2 could be made that can successfully generate the desired antibodies of the instant invention, because any random mutation or modification manifested within a TIMP-2 protein itself, or fragment thereof, would be predicted to adversely alter its biologically active 3-dimensional conformation, and therefore, the antigenic site itself, without undue experimentation to determine otherwise.

7. Claims 53-54 & 56 are rejected under 35 U.S.C. 102(e) as being unpatentable over Stetler-Stevenson et al. (U.S. Patent 5,595,885).

Stetler-Stevenson et al. teach antibodies made to the CSC-21K/TIMP-2 metalloproteinase inhibitor protein (e.g., col. 6, lines 43-67; col. 10, lines 24-32; col. 16, lines 34-58), in which specific peptide sequences/epitopes are described to make monoclonal antibodies (i.e., as it relates to claims 53-54). In that hybridoma cells are first required to be made, in order to generate such monoclonal antibodies, the limitations of claim 56 are also reasonably met by the teachings of Stetler-Stevenson; absent evidence to the contrary.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
May 30, 2002

PATRICIA A. DUFFY
PRIMARY EXAMINER